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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-4809; Draft Guidance for Industry on Applications Covered by Section 505(b)(2), 64 Federal Register No. 235 68697 (December 8, 1999)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled $1.5 billion.

For these reasons, we are very interested in commenting on the draft Guidance for Industry on Applications Covered by Section 505 (b)(2).

We commend the Food and Drug Administration's efforts to provide guidance to Industry on procedures for submitting a section 505(b)(2) application. However, there are several aspects of the draft guidance that require additional clarification.

1. Review Standard for Section 505(b)(2) Applications

In Section II. B. of the draft Guidance, the Agency describes the kinds of applications that are properly filed under section 505(b)(2); applications for new chemical entities/new molecular entities that rest in part on study data not conducted by the applicant or to which

the applicant has a no right of reference, and applications for changes to previously approved drugs. Applications that propose modifications to approved products may rely on the Agency's relevant previous findings of safety and effectiveness coupled with new studies conducted by the applicant or published data to support the section 505(b)(2) application. The Agency notes that the purpose of this use of section 505(b)(2) is to encourage innovation without requiring the re-demonstration of what has been demonstrated previously to FDA.

- **Comment and Recommendation**

  We acknowledge that the appropriate use of section 505(b)(2) applications can promote the efficient utilization of Agency and industry resources to the extent that the application seeks to rely on what has previously been demonstrated to the satisfaction of the high review standards of the Agency. However, to the extent that a section 505(b)(2) application seeks modifications or deviations from what has been shown to be previously safe and effective, the application must be reviewed with the same rigor applied to the application supporting the original innovator product. Even changes that seem minor may have a significant impact on safety and effectiveness. The Guidance should clarify and emphasize that the standard of review for proposed modifications under section 505(b)(2) is *identical* to the high review standard mandated by the Food Drug and Cosmetic Act to determine the safety and effectiveness for all other new drug applications and supplemental drug applications.

2. 505(b)(2) Applications for Combination Drug Products

In Section III of the draft Guidance, the Agency provides a list of examples of what types of changes to approved drugs could be appropriately submitted as 505(b)(2) applications. One example addresses products with multiple active ingredients, or combination products. Specifically, the draft states that a 505(b)(2) application would be appropriate for "[a]n application for a new combination product in which the active ingredients have been previously approved individually."

- **Comment and Recommendation**

  Individual active ingredients may be approved based on clinical proof of safety and efficacy as single therapeutic agents or, more rarely, as one part of a combination regimen. The Agency should clarify that a 505(b)(2) application for a new combination product using active ingredients which have been previously approved individually must contain clinical data demonstrating the safety and efficacy of the new combination, if the previous individually approved products were not labeled for combination use. Safety and efficacy data would also be required if the previous individually approved products were labeled for combination use, but the proposed 505(b)(2) product varies from the previously approved combination, e.g., in dosing regimen or strength. In addition, if a 505(b)(2) application proposes a fixed combination product based on previous individually approved products, additional safety and efficacy data would be required to demonstrate that the unitary formulation, its excipients and impurities do not adversely affect safety or efficacy.

Finally, any 505(b)(2) combination product would have to comply with the provisions of 21 C.F.R. § 300.50.

3. Studies Required to Support Modifications

In Section VII. of the draft Guidance, the Agency indicates that a section 505(b)(2) application must include "studies necessary to support the change or modification from the listed drug or drugs (if any)." The draft further states "complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s)." FDA states that it will provide guidance to the sponsor on identifying the appropriate bridging studies.

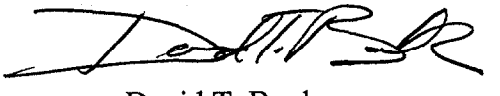
- **Comment and Recommendation**

  Agency guidance on clinical study plans to support proposed new drug applications is always welcomed and helpful to the sponsor. The Guidance, however, should include some general description of the kinds of studies needed to prove the safety and effectiveness of a section 505(b)(2) application. The Agency should not determine the sufficiency of supporting data solely on a case-by-case basis, merely reacting to the study plans submitted by the sponsors of proposed section 505(b)(c) applications. The review of the clinical data supporting these applications should be conducted in accordance with an articulated Agency policy. In addition, the policy should provide guidance on the threshold standards for the substance of supporting studies. Such a policy would greatly reduce the inconsistencies that may result from decisions based on *ad hoc* negotiations with sponsors of individual applications. Moreover, in evaluating the study plans submitted to support product modifications, FDA should consult with the

  innovator that developed the product to ensure that the proposed studies will lead to information necessary to ascertain whether the modified drug is safe and effective.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our comments and recommendations. We would be pleased to provide any additional information on this issue.

Sincerely,



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